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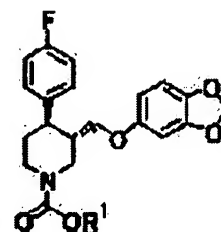
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(54) PRODUCTION OF CRYSTAL OF CARBAMATE COMPOUND

(57)Abstract:

PROBLEM TO BE SOLVED: To obtain the subject crystal having a high purity and useful as an intermediate of a medicine such as paroxetine as a treating agent of depression, etc., in a short process and by using an efficient means, by preparing a solution of a specific carbamate compound with a polar solvent and crystallizing out the carbamate from the solution with the polar solvent without changing the amount of the polar solvent substantially.

SOLUTION: This method for producing a crystal of a carbamate compound is provided by preparing a solution of a carbamate of the formula (R1 is a lower alkyl or the like) with a polar solvent, having preferably >10°C boiling point, then crystallizing out the above carbamate from the solution with the polar solvent without changing the amount of the polar solvent substantially to obtain the objective crystal. The above polar solvent is preferably a hydroxy compound of the formula: R3OH (R3 is a lower alkyl) (e.g. ethanol), etc. The compound of the formula is preferably obtained by reacting preferably (3S,4 R)-[5-(1,3-dioxaindanyl)-1-methylpiperidine with ethyl chloroformate in a solvent in the presence of a base.



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DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

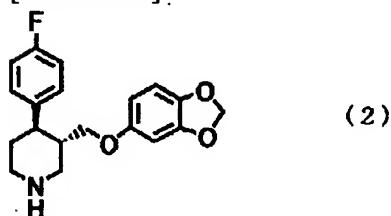
[Field of the Invention] This invention relates to the manufacture approach of the refined carver mate object crystal. The carver mate objects in this invention are compounds useful as intermediate fields, such as paroxetine useful as remedies, such as depression.

[0002]

[Description of the Prior Art] Generally the -3-[5-(1, 3-dioxo indanyl) oxymethyl]-4-(p-fluoro phenyl) piperidine expressed with a bottom type (2) (3S, 4R) is called paroxetine, has inhibitory action in 5-hydroxytryptamine (5-HT), and is an effective compound as a remedy of the illness of varieties, such as depression and Parkinson's disease.

[0003]

[Formula 3]



[0004] Until now, as the manufacture approach of paroxetine, (A) Christensen's and others approach (US4007196), (B) Sugi's and others approach (EP0812827A), the (C) kings' approach (JP,9-316072,A), etc. are reported.

[0005] The reaction rough liquid which phenyl chloroformate is made to react to N-methyl piperidine derivative [the compound whose R2 in a formula (3) is a methyl group] in a methylene chloride solvent, and includes a phenyl carver mate object [the compound whose R1 of a formula (1) is a phenyl group] by the approach of (A) is obtained. This reaction rough liquid was washed by the sodium hydroxide, then, was washed and dried with the hydrochloric acid, then the methylene chloride solvent was distilled off, and the solids-mixing object has been obtained. After dissolving in benzene and filtering this solids-mixing object furthermore, benzene is distilled off and residue is obtained, this residue, a potassium hydroxide, and methyl cellosolve are flowed back, and it flows back under reduced pressure, and water is added, benzene extracts, and the phenyl carver mate object is refined by distilling off benzene.

[0006] With the approach of (B), it is R1 of a formula (1). The benzyl carver mate object which is benzyl, Or R1 of a formula (1) Reaction rough liquid including t-butyl carver mate object which is t-butyl is obtained. This reaction rough liquid was put into water and toluene, the toluene layer was separated, the water layer was again extracted with toluene, the sodium-hydroxide water solution washed in accordance with the toluene layer, and it washed with water, and it dried and the oil-like benzyl carver mate object has been acquired by condensing.

[0007] With the approach of (C), it is R1 of a formula (1). R1 of the methyl carver mate object which is

a methyl group, or a formula (1) The ethyl carver mate object which is an ethyl group was made to generate, and the carver mate object of the shape of the shape of a solid-state and oil has been acquired by condensing a resultant.

[0008]

[Problem(s) to be Solved by the Invention] However, the following troubles were accepted in the conventional approach. Although various actuation was carried out by the approach of (A) and (B) in order to remove the impurity contained in a reaction rough product, this actuation is complicated from requiring many processes, and the phenyl carver mate object acquired as a result had the problem which does not necessarily become a high grade. Moreover, in order to pass through many processes, there was a problem to which yield falls. Moreover, the benzyl carver mate object acquired by the approach of (B) being oil-like, and having un-arranged on handling or product management.

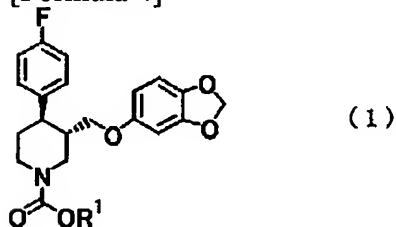
[0009] By the approach of (C), since it progresses to the following process only by condensing, the impurity mixed from a front process may remain also in the following process, or may do a bad influence. When the purpose compound manufactured using such intermediate field was used as drugs, purification of the purpose compound will take the effort and cost beyond the need in fact, and there was a big possibility that it might be connected disadvantageously.

[0010]

[Means for Solving the Problem] This invention is made that the above-mentioned trouble should be solved, are a short process and an efficient means, and offers the following approach of enabling purification of carver mate objects. That is, this invention offers the manufacture approach of the carver mate object crystal characterized by using as a polar-solvent solution the carver mate objects expressed with a bottom type (1), and carrying out crystallization of these carver mate objects from a polar-solvent solution, without next changing the amount of polar solvents substantially. However, R1 in a formula (1) A low-grade alkyl group and low-grade cycloalkyl radical, a low-grade alkenyl radical, an aralkyl radical, an aryl group, the alkyl group permuted by the univalent heterocycle radical, or the perfluoro-alkyl group of carbon numbers 1-6 is shown.

[0011]

[Formula 4]



[0012]

[Embodiment of the Invention] It is indicated as a compound (1) below carver mate object [expressed with the formula (1) in this invention. Also in other compounds, it is the same.] They are ** and a well-known compound. R1 in a compound (1) A low-grade alkyl group and low-grade cycloalkyl radical, a low-grade alkenyl radical, an aralkyl radical, an aryl group, the alkyl group permuted by the univalent heterocycle radical, or the perfluoro-alkyl group of carbon numbers 1-6 is shown.

[0013] In addition, in this specification, an organic radical says that carbon numbers are 1-8 with "it is low-grade." As a suitable example of a "low-grade alkyl group", a methyl group, an ethyl group, a propyl group, an isopropyl group, butyl, an isobutyl radical, t-butyl, a pentyl radical, or a hexyl group is mentioned.

[0014] As a suitable example of a "low-grade alkenyl radical", a vinyl group, an allyl group, 1-propenyl radical, etc. are mentioned, and a vinyl group is desirable. A "low-grade cycloalkyl radical" means the cycloalkyl radical whose carbon number of a ring is 3-6 pieces, and a cyclo propyl group, cyclo butyl, a cyclopentyl group, a cyclohexyl radical, etc. are mentioned as the suitable example.

[0015] An "aryl group" means a univalent aromatic hydrocarbon radical, and a phenyl group and a tolyl

group are mentioned as a suitable example of an aryl group. An aryl group may be an aryl group which has a substituent. As a suitable example of the aryl group which has a substituent, p-halophenyl radical, a mercapto (o-, m-, or p-) phenyl group, etc. are mentioned.

[0016] An aryl group permutation alkyl group is called "aralkyl radical." An aralkyl radical has the desirable radical whose carbon number of an alkyl group part is four or less, and benzyl, a benzhydryl group, a trityl radical, or a phenethyl radical is mentioned as the suitable example. Moreover, an aralkyl radical may be an aryl group in which an aryl group part has a substituent. The same radical as the above is mentioned as a suitable example of the aryl group which has this substituent.

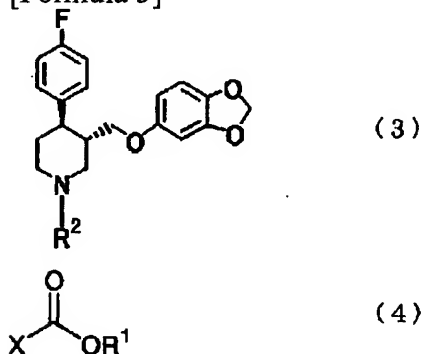
[0017] The radical by which the alkyl group whose carbon number is four or less was permuted by the univalent heterocycle radical as "an alkyl group permuted by the univalent heterocycle radical" is desirable. As a univalent heterocycle radical, the ring machine of 5 containing an oxygen atom, a nitrogen atom, or a sulfur atom or 6 membered-rings is desirable. As a suitable example of a univalent heterocycle radical, a pyrrolyl radical, an imidazolyl radical, a pyridyl radical, an indolyl radical, etc. are mentioned.

[0018] Especially if it receives by the well-known approach, it will not be limited, but the compound (1) in this invention is R1 of a compound (1). If it carries out, a low-grade alkyl group or an aralkyl radical is desirable. The compound (1) of a compound (1) manufactured by JP,9-316072,A, US4007196, EP0812827A, JP,6-47587,B, etc. by the approach of a publication is desirable, and what came to hand especially by the approach of JP,9-316072,A is still more desirable.

[0019] The compound (1) in this invention has [among these] the desirable compound (1) which the HAROGI acid ester expressed with a bottom type (4) to N-permutation piperidines expressed with a bottom type (3) was made to react to the bottom of existence of a base or un-existing in a solvent, and was obtained.

[0020]

[Formula 5]



[0021] However, R1 in a formula And R2 Independently, a low-grade alkyl group and low-grade cycloalkyl radical, a low-grade alkenyl radical, an aralkyl radical, an aryl group, the alkyl group permuted by the univalent heterocycle radical, or the perfluoro-alkyl group of carbon numbers 1-6 is shown, and X shows a halogen atom, respectively. R2 of a compound (3) A methyl group, an ethyl group, or t-butyl is desirable. X of a compound (4) has a chlorine atom or a desirable bromine atom.

[0022] The following compound is mentioned as an example of a compound (3). AnR [3] and (R[4]) - 3-[5-(1, 3-dioxa indanyl) oxymethyl]-4-(p-fluoro phenyl)-1-methyl piperidine, AnR [3] and (R[4]) - 3-[5-(1, 3-dioxa indanyl) oxymethyl]-4-(p-fluoro phenyl)-1-ethyl piperidine, R [3] and (R[4]) - 3-[5-(1, 3-dioxa indanyl) oxymethyl]-4-(p-fluoro phenyl)-1-(t-butyl) piperidine.

[0023] The following compound is mentioned as an example of a compound (4). KUROROGI acid methyl, ethyl chloroformate, KUROROGI acid t-butyl, phenyl chloroformate, KUROROGI acid benzyl, KUROROGI acid trifluoromethyl, KUROROGI acid cyclohexyl.

[0024] As a solvent used for the reaction of a compound (3) and a compound (4), a methylene chloride, chloroform, diethylether, t-butyl methyl ether, a tetrahydrofuran, 1,4-dioxane, 1, 2-dimethoxyethane, benzene, toluene, a xylene, a hexane, a heptane, the petroleum ether, methyl acetate, ethyl acetate, N.N-

dimethylformamide, or N,N-dimethylacetamide is desirable, and especially toluene or a tetrahydrofuran is desirable.

[0025] As a base in the case of using a base in the reaction of a compound (3) and a compound (4), organic amines, alkoxides, an alkali-metal hydroxide, an alkaline-earth-metal hydroxide, an alkali-metal hydride, an alkaline-earth-metal hydride, or a carbonate is desirable.

[0026] The HAROGI acid ester expressed with a formula (4) to N-permutation piperidines which the compound (1) obtained at various reactions is used as a compound (1) in this invention, and are expressed with a formula (3) in a solvent. It is desirable to use what filtered the reaction rough product which was made to react to the bottom of existence of a base or un-existing, and was obtained when a solid-state was in a system, or condensed it as it was. The compound after concentration (1) may be a solid-state, or may be oil-like.

[0027] Furthermore, in order to perform the approach of this invention efficiently, as for a compound (1), it is desirable to use that whose amount of impurities at the time of expressing by area % in high speed liquid chromatography (HPLC) is under 5 area %. When the amount of impurities in this compound (1) is more than 5 area %, it is desirable to repeat the approach of this invention twice or more, or to perform easy purification, and to carry out purity to more than 95 area %.

[0028] The compound (1) in this invention is R1. The compound (1) which is a low-grade alkyl group is desirable, and it is R1 especially. The compound (1) which are a methyl group, an ethyl group, and t-butyl is desirable.

[0029] In this invention, a compound (1) is first used as a polar-solvent solution. That whose dipole moments are 1.5-1.8 as a polar solvent is desirable, and that especially whose dipole moments are 1.6-1.7 desirable. The boiling point of a polar-solvent solution has that still more desirable of super-***** [degrees C / 10].

[0030] Furthermore, as a polar solvent, the mixed solvent of the hydroxy compound expressed with R3 OH (however, R3 shows a low-grade alkyl group.) or this hydroxy compound, and water is desirable. R3 of a hydroxy compound expressed with R3 OH A methyl group, an ethyl group, or especially an isopropyl group is desirable. When it is a mixed solvent, it is desirable to make the amount of the water to a hydroxy compound into weight 0 ** - 1 time, and it is desirable that it takes especially for weight 0 ** - 0.5 times. More than the 4 time weight of the amount of polar solvents is desirable to a compound (1), and especially its 5 - 16 time weight is desirable.

[0031] As the preparation approach of the polar-solvent solution of a compound (1), a compound (1) is added to a polar solvent, or a compound (1) is added to a polar solvent, for example, this is made into suitable temperature, and the approach of agitating if needed and dissolving a compound (1) is mentioned. As suitable temperature at the time of considering as a polar-solvent solution, 10 degrees C or more and under the boiling point of a polar solvent are desirable, and especially 20-60 degrees C are desirable.

[0032] Furthermore, in this invention, crystallization of the compound (1) is carried out from a polar-solvent solution. As the approach of crystallization, it is desirable to carry out with the so-called cooling method, and the method of depositing a crystal is desirable by cooling and leaving a polar-solvent solution below the temperature at the time of the dissolution of a compound (1) to desirable temperature lower 50 degrees C than the temperature at the time of the dissolution. The temperature at the time of cooling has -20 degrees C - desirable +20 degrees C, and is desirable. [of -10 degrees C - especially +10 degrees C] Moreover, neglect time amount has 12 - 72 desirable hours, and is especially desirable. [of 24 - 48 hours]

[0033] The crystal of the compound (1) according to the compound (1) made into the purpose may be added to a polar-solvent solution as seed crystal. Time amount required for crystallization can be shortened by adding seed crystal. Especially the amount of seed crystal is not limited.

[0034] In this invention, it differs from the approach by the conventional concentration in the point to which crystallization of the compound (1) is carried out, without changing the amount of polar solvents substantially. As for the rate of change of the amount of polar solvents, it is desirable that it is less than [extent which changes with volatilization or moisture absorption, or it, -5 % of the weight (amount

which decreased 5% of the weight rather than polar-solvent weight at time of the dissolution) - its +5 % of the weight (amount which increased 5% of the weight from the polar-solvent weight at the time of the dissolution) is especially desirable, and -2 % of the weight (amount which decreased 2% of the weight rather than polar-solvent weight at time of the dissolution) - its **0 % of the weight is especially desirable.

[0035] As for the crystal of the obtained compound (1), it is desirable that the polar solvent which extracted by the filtration approaches, such as the Kiriya filtration, and then was cooled washes. The temperature of a penetrant remover has -20 degrees C - desirable 20 degrees C, and is desirable. [of -10 degrees C - especially 10 degrees C] Moreover, more than the actual size weight of the amount of penetrant removers is desirable to a rough compound (1), and especially its 1.5 - 2.0 time weight is desirable. Furthermore, as for a crystal, it is desirable to make it dry, and it is desirable to consider as 24 hours or more at the temperature of 20-50 degrees C as desiccation conditions. Drying under vacuum conditions furthermore is desirable.

[0036] In this invention, the crystal of the compound (1) of a high grade is obtained by carrying out crystallization of the compound (1) from a polar-solvent solution. As for the compound (1) of the high grade obtained by the approach of this invention, it is desirable that the amount of impurities at the time of expressing by area % in HPLC is 0 - 0.01%. It means that an impurity is not substantially detected in HPLC as this amount of impurities is 0%, i.e., a compound (1) does not contain an impurity detectable by HPLC. It is desirable that the purity of the crystal of a compound (1) repeats the approach of this invention to 0.01% super-***** case according to the purpose. The crystal of the compound (1) obtained by this invention is the optimal as a raw material of especially physic [be / it / the crystal of a high grade].

[0037]

[Example] This invention is not limited by these, although an example is given to below and this invention is concretely explained to it. In addition, the analysis conditions of HPLC indicated in the example are as follows.

Column: YMC ODS-AM AM-312 150mmx6.0mm, I.D.S-5UM 120A.

Eluate: A 0.1% trifluoroacetic acid water solution / acetonitrile =1/4.

The rate of flow: 1 mL/min.

Detector: UV (293nm).

Injection rate: They are 10mL(s) about the polar-solvent solution which contains a compound (1) by 1 mg/mL.

[0038] 3S and (R[4])-[5-(1, 3-dioxindanyl) oxymethyl]-4-(p-fluorophenyl)-1-methyl piperidine 1g was melted to [example 1 of reference] dehydration tetrahydrofuran 20mL, and ethyl chloroformate 2.87mL was gradually added under ice-cooling. After carrying out overnight heating with a 70-degree C oil bath, 4.4g of potassium carbonate was added and heating was continued for two days. Ethanol was added and filtered to the reaction mixture, the filtrate was condensed, and 1.22g of an oil-like ethyl carver mate object (compound whose R1 is an ethyl group (1)) was obtained.

[0039] 3S and (R[4])-[5-(1, 3-dioxindanyl) oxymethyl]-4-(p-fluorophenyl)-1-methyl piperidine 1g was melted to [example 2 of reference] dehydration tetrahydrofuran 20mL, and phenyl chloroformate 3.77mL was gradually added under ice-cooling. After carrying out overnight heating with a 70-degree C oil bath, 4.4g of potassium carbonate was added and heating was continued for two days. Ethanol was added and filtered to the reaction mixture, the filtrate was condensed, and 1.36g (compound whose R1 is a phenyl group (1)) of oil-like phenyl carver mate objects was acquired.

[0040] 20g (purity 98 area %) of ethyl carver mate objects acquired in the example 1 of [example 1] reference was added to the mixed solvent of ethanol 100cc and 20 cc of water, they were agitated, and it was made to dissolve at 25 degrees C. the crystal obtained after keeping it for 30 hours in the refrigerator kept at 5 degrees C -- filtering -- 5-degree C ethanol 20cc -- come out -- slag was washed, **** was dried under vacuum for 24 hours, and 18g of white crystals was obtained. As a result of analyzing by HPLC, purity was 100 area % (namely, the amount of impurities 0 area %). Moreover, the melting point of a white crystal was 62 degrees C.

[0041] 20g (HPLC purity 98 area %) of ethyl carver mate objects acquired in the example 1 of [example 2] reference was added to the mixed solvent of isopropyl alcohol 170cc and 50 cc of water, they were agitated, and it was made to dissolve at 25 degrees C. the crystal obtained after keeping it for 30 hours in the refrigerator kept at 5 degrees C -- filtering -- 5-degree C isopropyl alcohol 20cc -- come out -- slag was washed, **** was dried under vacuum for 24 hours, and 17.0g of white crystals was obtained. As a result of analyzing by HPLC, purity was 100 area % (namely, the amount of impurities 0 area %).

Moreover, the melting point of a white crystal was 62 degrees C.

[0042] 20g (HPLC purity 98 area %) of ethyl carver mate objects acquired in the example 1 of [example 3] reference was added to isopropyl alcohol 100cc, they were agitated, and it was made to dissolve at 25 degrees C. the crystal obtained after keeping it for 30 hours in the refrigerator kept at 5 degrees C -- filtering -- cold 5-degree C isopropyl alcohol 20cc -- come out -- slag was washed, **** was dried under vacuum for 24 hours, and 16.0g of white crystals was obtained. As a result of analyzing by HPLC, purity was 100 area % (namely, the amount of impurities 0 area %). Moreover, the melting point of a white crystal was 62 degrees C.

[0043] R1 in a [example 4] compound (1) 20g (HPLC purity 95 area %) of compounds which are t-butyl was added to the mixed solvent of isopropyl alcohol 180cc and 60 cc of water, they were agitated, and it was made to dissolve at 30 degrees C. the crystal obtained after keeping it for 30 hours in the refrigerator kept at 5 degrees C -- filtering -- 5-degree C isopropyl alcohol 20cc -- come out -- slag was washed, **** was dried under vacuum for 24 hours, and 16.4g of white crystals was obtained. As a result of analyzing by HPLC, purity was 100 area % (namely, the amount of impurities 0 area %).

Moreover, the melting point of a white crystal was 76 degrees C.

[0044] Adding 20g (HPLC purity 98 area %) of phenyl carver mate objects acquired in the example 2 of [example 5] reference to isopropyl alcohol 200cc, and agitating them, the temperature up was carried out and it was made to dissolve to 75 degrees C. the crystal which was able to acquire the temperature up after carrying out natural radiationnal cooling for 24 hours, a stop and -- filtering -- 5-degree C isopropyl alcohol 20cc -- come out -- slag was washed, **** was dried under vacuum for 24 hours, and 19.9g of white crystals was obtained. As a result of analyzing by HPLC, purity was 100 area % (namely, the amount of impurities 0 area %). Moreover, the melting point of a white crystal was 107 degrees C.

[0045] 20g (purity 98 area %) of ethyl carver mate objects acquired in the example 1 of [example 6] reference was added to the mixed solvent of ethanol 100cc and 20 cc of water, they were agitated, and it was made to dissolve at 25 degrees C. the crystal obtained after keeping it for 24 hours in the refrigerator which added some crystals obtained in the example 1 as seed crystal, and was kept at 5 degrees C -- filtering -- 5-degree C ethanol 20cc -- come out -- slag was washed, **** was dried under vacuum for 24 hours, and 18g of white crystals was obtained. As a result of analyzing by HPLC, purity was 100 area % (namely, the amount of impurities 0 area %). Moreover, the melting point of a white crystal was 62 degrees C.

[0046] 20g (HPLC purity 98 area %) of ethyl carver mate objects acquired in the example 1 of [example 7] reference was added to the mixed solvent of isopropyl alcohol 170cc and 50 cc of water, they were agitated, and it was made to dissolve under a room temperature. the crystal obtained after keeping it for 24 hours in the refrigerator which added some crystals obtained in the example 2 as seed crystal, and was kept at 5 degrees C -- filtering -- 5-degree C isopropyl alcohol 20cc -- come out -- slag was washed, **** was dried under vacuum for 24 hours, and 17.0g of white crystals was obtained. As a result of analyzing by HPLC, purity was 100 area % (namely, the amount of impurities 0 area %). Moreover, the melting point of a white crystal was 62 degrees C.

[0047] 20g (HPLC purity 98 area %) of ethyl carver mate objects acquired in the example 1 of [example 8] reference was added to isopropyl alcohol 100cc, they were agitated, and it was made to dissolve under a room temperature. the crystal obtained after keeping it for 24 hours in the refrigerator which added some crystals obtained in the example 3 as seed crystal, and was kept at 5 degrees C -- filtering -- 5-degree C isopropyl alcohol 20cc -- come out -- slag was washed, **** was dried under vacuum for 24 hours, and 16.0g of white crystals was obtained. As a result of analyzing by HPLC, purity was 100 area % (namely, the amount of impurities 0 area %). Moreover, the melting point of a white crystal was 62

degrees C.

[0048] R1 in a [example 9] compound (1) 20g (HPLC purity 95 area %) of compounds which are t-butyl was added to the mixed solvent of isopropyl alcohol 180cc and 60 cc of water, they were agitated, and it was made to dissolve under a room temperature. the crystal obtained after keeping it for 24 hours in the refrigerator which added some crystals obtained in the example 4 as seed crystal, and was kept at 5 degrees C -- filtering -- 5-degree C isopropyl alcohol 20cc -- come out -- slag was washed, **** was dried under vacuum for 24 hours, and 16.4g of white crystals was obtained. As a result of analyzing by HPLC, purity was 100 area % (namely, the amount of impurities 0 area %). Moreover, the melting point of a white crystal was 76 degrees C.

[0049] Adding 20g (HPLC purity 98 area %) of phenyl carver mate objects acquired in the example 2 of [example 10] reference to isopropyl alcohol 200cc, and agitating them, the temperature up was carried out and it was made to dissolve to 75 degrees C. After even 50 degrees C even of stops cooled the temperature up, it was left having added some crystals obtained in the example 5 as seed crystal, and keeping at 20 degrees C for 24 hours. the obtained crystal -- filtering -- 5-degree C isopropyl alcohol 20cc -- come out -- slag was washed, the vacuum drying of the **** was carried out, and 19.9g of white crystals was obtained. As a result of analyzing by HPLC, purity was 100 area % (namely, the amount of impurities 0 area %). Moreover, the melting point of a white crystal was 107 degrees C.

[0050]

[Effect of the Invention] According to the approach of this invention, the crystal of the compound (1) of a high grade can be obtained only by adding and leaving a polar solvent to the compound (1) obtained by the production process. The crystal of the compound (1) obtained by this approach is a crystal of the high grade which does not contain an impurity substantially. Therefore, the crystal of the compound (1) obtained by the approach of this invention is the compound of high quality as intermediate field of drugs. When it reacts using the crystal of this compound (1), there is an advantage which can react efficiently and can skip an excessive purification process. Furthermore, the crystal of the compound (1) obtained by the approach of this invention is useful as intermediate field of various useful drugs.

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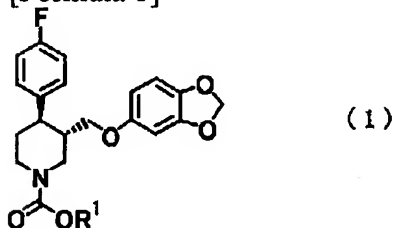
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CLAIMS

[Claim(s)]

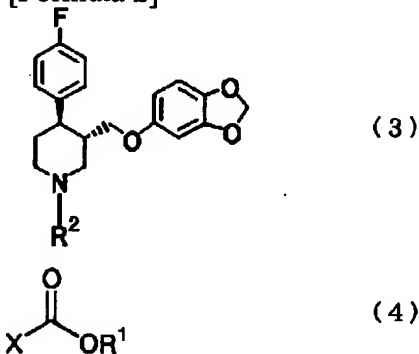
[Claim 1] The manufacture approach of the carver mate object crystal characterized by using as a polar-solvent solution the carver mate objects expressed with a bottom type (1), and carrying out crystallization of these carver mate objects from a polar-solvent solution, without next changing the amount of polar solvents substantially. However, R1 in a formula (1) A low-grade alkyl group and low-grade cycloalkyl radical, a low-grade alkenyl radical, an aralkyl radical, an aryl group, the alkyl group permuted by the univalent heterocycle radical, or the perfluoro-alkyl group of carbon numbers 1-6 is shown.

[Formula 1]



[Claim 2] The manufacture approach according to claim 1 which uses as a polar-solvent solution the carver mate objects which obtained in the solvent the HAROGI acid ester expressed with a bottom type (4) to N-permutation piperidines expressed with a bottom type (3) by making it react to the bottom of existence of a base or un-existing. However, R1 in a formula And R2 Independently, a low-grade alkyl group and low-grade cycloalkyl radical, a low-grade alkenyl radical, an aralkyl radical, an aryl group, the alkyl group permuted by the univalent heterocycle radical, or the perfluoro-alkyl group of carbon numbers 1-6 is shown, and X shows a halogen atom, respectively.

[Formula 2]



[Claim 3] The manufacture approach according to claim 1 or 2 of adding the seed crystal of carver mate objects to a polar-solvent solution.

[Claim 4] The manufacture approach given [the boiling point of a polar-solvent solution] in 10-degree-

super-***** claims 1, 2, or 3.

[Claim 5] The manufacture approach according to claim 3 that the temperature at the time of considering as a polar-solvent solution is 10 degrees C or more and under the boiling point of a polar solvent.

[Claim 6] R1 The manufacture approach according to claim 1 to 5 which is a methyl group, an ethyl group, t-butyl, or a phenyl group.

[Claim 7] The manufacture approach according to claim 1 to 6 that a polar solvent is a mixed solvent of the hydroxy compound expressed with R3 OH (however, R3 shows a low-grade alkyl group.) or this hydroxy compound, and water.

[Claim 8] The manufacture approach according to claim 1 to 7 that the amount of impurities contained during a carver mate object crystal is 0 - 0.01% (area % in high speed liquid chromatography).

[Translation done.]